The specification has been amended to make reference to the International Application from which this case derives. As regards the Examiner's objection in item 8, attention is directed to the fact that claim 3 as filed and published provides base for "effector domain is a chimeric domain" which is the wording used by the claims.

An Abstract of the Disclosure has been provided, as requested.

The claims have been revised to define the invention with additional clarity. The claims as presented find support, for example, as follows:

claim 32 – claims 1, 3 and 7

claim 33 – claim 8 and page 14, line 6 and reference therein to Figure 17

claim 34 – claim 9 and page 10, lines 5 and 6

claim 35 – claims 10 and 3

claim 36 – claim 11

claim 37 – claim 12

claim 38 – claim 14

claim 39 – claim 15 and page 5, line 25

claim 40 – claim 30

claim 41 – claims 1, 3 and 7 (see also page 11, lines 25-32 and page 14, lines 1-4)

claim 42 – claim 8

claim 43 – claim 9 and page 10, lines 5 and 6

claim 44 – claims 10 and 3

claim 45 – claim 11

claim 46 – claim 12

claim 47 – claim 14

claim 48 – claim 15 and page 5, line 25

claim 49 – claim 30.

That the claims have been revised should not be taken as an indication that Applicants agree with any view expressed by the Examiner. Rather, the revisions are offered merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

As regards the requirement for restriction, the Examiner is again urged to reconsider his/her position for the reasons provided in the Response filed April 8, 2002 (those arguments being incorporated herein by reference) and further in view of the comments that follow.

In requiring restriction initially the Examiner cited Cole et al. The Examiner now makes reference to Cole et al and Greenwood et al.

The arguments presented April 8, 2002 in response to the restriction requirement still apply. The present invention is based on work in which the constant ("effector") regions of immunoglobulins were engineered in order to combine and manipulate their effector functions. As distinct from the prior art, this was done by multiple point mutations, in specific regions using only residues present in other immunoglobulins rather than using either (i) non-natural mutations, or (ii) wholesale grafting of regions. This has the advantage of producing molecules that are as 'natural' as possible, avoiding the introduction of potentially immunogenic regions, while also precisely controlling the effector functions which result. Such an approach has not been taken in any of the prior art of which Applicants are aware. Although the claims have now been split, this is still no justification for lack of unity in the variable region.

In essence, the Examiner's argument appears to be that since Cole et al and Greenwood et al allegedly disclose an effector region falling within the scope of the claim, all generic definitions in the claim were irrevocably disunified. Applicants submit that this is wrong in principle, since that would mean (to take a hypothetical situation) even if the USPTO were to accept a narrow genus (or even a single sequence) of effector molecules as being novel and unobvious *per se*, then Applicants would still need a different patent application for each variable region linked to it, despite the fact that the former is the invention here - the latter is simply the way it can be applied by those skilled in the art. Unless an infinite number of cases were filed, the patent could always be avoided simply by anybody choosing to use it with a different variable binding site function. (The situation is analogous to someone inventing a new and unobvious engine for an automobile, and having to file a separate application for each different automobile in which it is used.)

Importantly, effector functions are, to all intents and purposes, independent of the variable binding site functions. This is illustrated in the attached table (Appendix III). The table shows the result obtained for each 'effector' mutation upon which the present claims are based (Δab, Δac, Δa) on various effector functions (given in the first column). In almost all cases, the tests were done using at least two different variable region specificities (selected from CAMPATH-1, Fog-1, B2 and 2D10, in the last column). In all cases where variable regions were compared, a common improvement in effector function, which correlates with the constant region, is apparent in the different specificities. The improvements in effector function are achieved irrespective of variable region specificity.

Thus, it is submitted that the arguments about the patentability or otherwise of the 'effector' invention should not affect the unity of the variable regions to which it is attached. Nevertheless, for completeness the following comments are offered regarding Cole et al. and Greenwood et al.

As regards Cole et al, extensive arguments were provided in the April 8, 2002 Response. The Examiner disputes these saying (page 2) that binding specificity is not a feature of the claims, and also that Cole et al discloses an IgG2 wherein (see Action, pg 2, 8th line from bottom):

> "at least 2 amino acids at position 234 and 235 have been modified to V and A, respectively (See page 3615, Table 1, in particular). The said effector domain is capable of specifically binding to FcγIIb".

Respectfully, this statement is simply wrong. The original claim required that the amino acids be modified in the region in question. Modifications in the Cole et al table are underlined, and no single molecule has been modified to a V and an A. Cole et al's V234 and A235 are IgG2 native. Also, for completeness, the molecules of Cole et al have not been shown to bind FcRn and\or FcγRIIb.

As far as Applicants can discern, no novelty objection over Cole et al made in the present Action. This indicates that the Examiner has accepted Applicants arguments and this repeated unity objection over Cole et al is seemingly included in error. That being the case, the finality of the requirement for restriction is improper and the Examiner is urged to consider the following comments regarding Greenwood et al.

Greenwood et al is co-authored by one of the instant Applicants and is acknowledged in the application on page 8. It should be noted at the outset that this is

based on a different technology, namely domain switching, and had different aims than those of the present invention.

Also, it is not a matter of record whether any or all of the Greenwood et al mutants are actually capable of binding FcRn and\or FcγIIb - which is a key feature of the current invention.

Nevertheless, in order to more clearly and unambiguously distinguish over Greenwood et al, the present claims have now been limited to require either 233P, 234V, 235A and 236 [G or no residue]. This clearly excludes all embodiments of Greenwood et al. (See also comments that follow).

In view of the above, the Examiner is again requested to withdraw the requirement for restriction.

Claims 1-15 and 30 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. The rejection is traversed.

The Examiner cites various documents to support the lack of predictability in the art. Of these, Ngo et al, Kuby et al and Riechmann et al seem to be cited to support a rather general 'sequence\function' proposition, rather than any particular point.

The citations referred to by the Examiner do no more than show that some experimentation may be necessary. Considering the *In re Wands* criteria, it must be remembered that merely because some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive." Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 224 USPQ 409, 413 (CAFC 1984). Indeed, in Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384-1385, 231 USPQ 81, 94 (CAFC 1986), the Federal Circuit found, on that basis, that the

experimentation required was not "undue". Like the present case, that case also involved generic claims based on hybridoma technology, and was judged against a level of skill in the art almost 20 years earlier than the present case.

In any case, some of the objections are now moot in view of the amendments to the claims, which specify particular amino acids which must be present in the effector domain.

The table presented herewith (Appendix III) makes it clear that the effector-domain invention can be practiced with different variable regions (all from antibodies, as now required by the claim) without loss of the advantages it offers. Thus, no undue experimentation would be required to pair it with different variable regions according to choice. The documents cited in relation to the antibody (variable binding site) specificity are irrelevant.

It is submitted that where the invention exists as a result of the combination (albeit non-obvious combination) of well known techniques, enablement can be satisfied with little experimentation. This has been clearly stated in In re Strahilevitz, 212 USPQ 561 (CCPA 1982) wherein the court held that a broad immunological method claim having "nearly universal applicability" was enabled even without specific working examples. In the present case, there are many working examples.

Therefore, Applicants submit that the skilled molecular biologist, in the light of the present disclosure, can prepare specific binding molecules, e.g., using hybridoma technology expressing an antibody against any target antigen of interest. Having specified the key residues in the constant region to change to give the improved properties (which are required by the claim), it is within the ambit of the skilled person to

practice the invention throughout the scope of the claims. As stated by the Federal Circuit in Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (CAFC 1986), "a patent need not teach, and preferably omits, what is well known in the art".

Reconsideration is requested.

Claims 1-15 and 30 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. The rejection is traversed.

Examiner cites the Guidelines of Friday, January 5, 2001. Examiner's attention is drawn to said guidelines which state:

> "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient" (*See Eli Lilly*, 119 F.3d at 1568, USPQ2d at 1406.)

The present claims provide just such a combination of structural and functional characteristics.

The following is taken from Example 16 of the "SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES".

"The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five

isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein."

In the Example given in the Guidelines, an antibody described purely by its binding specificity was deemed to satisfy the Written Description requirement. The present case discloses several example constant regions and a narrow genus is claimed based closely on these. Thus, compared with the Example, it contains considerably more information in support of a claim containing many more limitations.

Reconsideration is requested.

Claims 1, 4, 9, 13 and 15 stand rejected under 35 USC 112, second paragraph. Withdrawal of the rejection is in order in view of the above claim revisions and comments that follow.

"Substantially null-allotypic" would be understood by those skilled in the art, particularly in view of the cross reference to WO 92/16562 (page 14, lines 29-30).

It is established that "if the claims, read in light of the specification, reasonably appraise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (CAFC 1986). That is the case here.

Regarding "binding site," in the context of a binding molecule the phrase is unambiguous in referring to the hypervariable region of antibody, rather than its target.

"Campath" has been replaced by reference to the CD52 antigen is found on human lymphocytes.

Reconsideration is requested.

Claims 1-3, 5-7, 11-15 and 30 stand rejected under 35 USC 102(b) as anticipated by Greenwood et al. The rejection is traversed.

First and foremost, although the claims always included a functional requirement that the effector domain bind to FcRn or FcγIIb, there is no evidence of record which shows that the mutants of the citation do this. The Examiner's argument in this respect (top of page 17) appears to be pure assertion.

In any case, the claims as now presented clearly distinguish over Greenwood et al. Referring to the reference, Figure 1, only the DS111/41 and DS444/14 mutants have modified CH2 regions. It can be inferred from the citation that neither of these have the sequence required by the claims, i.e., 233P, 234V, 235A and 236[G or deleted] and 327G, 330S and 331S.

Appendix IV provided herewith shows a line-up of some sequences relevant to the present case. DS111/41 is shown therein.

Reconsideration is requested.

Claims 1, 4, 8 and 10 stand rejected under 35 USC 103 as obvious over Greenwood et al, Morgan et al or Chappel et al or Cole et al. The rejection is traversed.

The independent claims are now based on the residues specified in prior claim 8. However, none of the documents cited by the Examiner, or legitimate combinations of

these documents, would have suggested the combination of residues now specified in the claims.

Greenwood et al is concerned only with the effector functions ADCC and complement lysis. Thus even the 'closest' mutants prepared (DS111/41 and DS1141) differ in the identity of the 233-236 residues which are required by the claims and also include several changes that are irrelevant to the present invention (274, 296, 300, 309 and 339) (see Appendix IV).

Interestingly, a comparison between Fig 3 of Greenwood et al and the present application (Fig 9 and 10a for CAMPATH and Fog-1 respectively) suggests that even in respect of ADCC, the mutants of the citation are inferior to some of the preferred mutants of the present invention (e.g., none of the Greenwood et al mutants improve over IgG4).

By comparing:

G1Δb, G1Δc, G1Δab, and G1Δac, with

G1Δa or D2's DS111/41 and DS1141

it seems that the 233-236 residues are an important factor in ADCC, which is not taught or suggested by Greenwood et al.

More importantly, however, Greenwood et al is entirely silent in respect of the other effector functions required by the claims, i.e., does not even teach (i) the desirability of balancing these other functions (FcRn and\or FcγRIIb), (ii) the mutations which would achieve the desired functions, or (iii) whether making "extra" mutations would negate or affect the ADCC and lysis functions. The present invention addresses all of these points.

Examiner states (Action page 16) that:

> "Greenwood *et al* teach that it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy...."

but this is scarcely a teaching or even an indication of how all such antibodies can be prepared, and Applicants submit it is simply untenable to assert that this statement would have rendered all such improved antibodies "obvious".

Morgan et al is concerned with C1q, FcγRI, and FcγRIII binding. As with Greenwood et al above, this citation is not primarily concerned with other effector functions required by the claims (e.g., minimizing ADCC - indeed see the relatively poor results given in Figure 4 for the mutants taught)

Certainly it does not teach (i) the desirability of balancing these and other functions (FcRn and\or FcγRIIb), (ii) the mutations which would achieve the desired functions, or (iii) whether making "extra" mutations would negate or affect the other functions elsewhere in the molecule. Thus there is nothing which would lead one of ordinary skill in the art to combine Morgan et al with Greenwood et al, and even if such a combination had been made, this teaching would not have resulted.

Regarding the comment on page 18 line 13 "....still capable of binding to FcRn such as FcgRI", Applicants do not understand this remark. As the Examiner is no doubt aware, these receptors and effector functions are quite distinct (see pages 2-3 of the present application).

Chappel et al is, as the title suggests, an attempt to identify the FcγRI binding site using IgG1 and IgG2 sequences. The authors correctly focussed attention on the lower hinge region sequences. However, unlike the present invention, Chappel et al was

concerned only with the high affinity receptor FcgRI, and not the low affinity receptors. Additionally, unlike the present invention, the citation used primarily single point mutation, or swapping the entire CH2 domain (10 changes), rather than the combinations of point mutations taken from other wild-type IgG sequences.

As regards Cole et al, extensive arguments were given in the previous response, and this citation is also discussed above in relation to unity, all such comments being incorporated here by reference.

In conclusion, Applicants do not deny that, individually, each residue specified in the claim will appear in the literature (indeed, since they are all wild-type residues from different IgGs, it is inevitable they will appear, individually, or in sub-groups, in thousands of publications). Likewise there is a literature on each of the effector functions, since Applicants did not invent those individual functions, or even discover them. However, nobody had previously thought to combine those functions using the precise combinations of mutations specified in the present claims, and none of the documents cited by the examiner would have lead the skilled person to do that. The Examiner's assertion on page 20 of the Action, final paragraph, that combining the cited art would give one of ordinary skill in the art a reasonable expectation of producing [prior claim 8] is just that - an assertion. A combination of these 4 documents could give virtually anything (or everything) in terms of mutated CH2 regions but that would not have made all mutant CH2 regions obvious.

To establish obviousness under Section 103,

> "[b]oth the suggestion and the expectation of success must be founded on the prior art and not in applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ 1529, 1531 (Fed. Cir. 1988).

A fair reading of the prior art documents alone, without *ex post facto* analysis, shows that it could not reasonably have been expected that one or ordinary skill in the art would have arrived at the present invention.

> "At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness. . . ." *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993) (citations omitted).

Withdrawal of the rejection of the claims as obvious is clearly in order and same is requested.

Claim 9 stand rejected under 35 USC 103 as obvious over Greenwood et al in view of WO 95/05468. The rejection is traversed.

Although not agreeing with the Examiner's assertion, Applicants submit this rejection is moot since the relevant claims depend from claims which are novel and inventive.

Reconsideration is requested.

Claims 14 and 15 stand rejected under 35 USC 103 as obvious over Greenwood et al in view of USP '063. The rejection is traversed.

Although not agreeing with the Examiner's assertion, Applicants submit this rejection is moot since the relevant claims depend from claims which are novel and unobvious.

Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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iii) Appendix III - Table of unity

Effects of Δab and Δac mutations on IgG1 activity and of Δa mutation on IgG2 activity in various test systems. The variable regions contexts in which the constant regions were tested are listed. They are CAMPATH-1 (CD52 specificity), Fog-1 (anti-RhD), B2 (anti-human platelet antigen-1a) and 2D10 (anti-vascular adhesion protein-1). The reductions in activity given represent the approximate increase in antibody concentration necessary to achieve the same level of activity as IgG1 or IgG2.

IgG1Δab = 233P, 234V, 235A and 236- and 327G, 330S and 331S present in the tested molecule.
IgG1Δac = 233P, 234V, 235A and 236G and 327G, 330S and 331S present in the tested molecule.
IgG2Δa = 233P, 234V, 235A and 236- and 327G, 330S and 331S present in the tested molecule.

(see patent application Figure 15)

Function	Effect on Δab mutation on IgG1 activity	Variable regions with which tested
Binding to:		
FcγRI	10^4-fold reduction to background	CAMPATH-1, Fog-1, B2
FcγRIIa 131R	8-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIa 131H	16-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIb1*	4-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIIb NA1	>100-fold reduction to background	Fog-1, B2
FcγRIIIb NA2	>100-fold reduction to background	Fog-1, B2
Monocyte activation	100-fold reduction	Fog-1, B2
Complement lysis	>50-fold reduction to background	CAMPATH-1
ADCC	>100-fold reduction to background	CAMPATH-1, Fog-1

Function	Effect on Δac mutation on IgG1 activity	Variable regions with which tested
Binding to:		
FcγRI	10^4-fold reduction to background	CAMPATH-1, Fog-1, B2
FcγRIIa 131R	10-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIa 131H	32-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIb1*	4-fold reduction	CAMPATH-1, Fog-1, B2
FcγRIIIb NA1	>100-fold reduction to background	Fog-1, B2
FcγRIIIb NA2	>100-fold reduction to background	Fog-1, B2
Monocyte activation	100-fold reduction	Fog-1, B2
Complement lysis	>50-fold reduction to background	CAMPATH-1

ADCC	>100-fold reduction to background	CAMPATH-1, Fog-1

Function	Effect on Δa mutation on IgG2 activity	Variable regions with which tested
Binding to:		
FcγRI	remained at background	CAMPATH-1, Fog-1, 2D10
FcγRIIa 131R	no effect	CAMPATH-1, Fog-1, 2D10
FcγRIIa 131H	8-fold reduction	CAMPATH-1, Fog-1, 2D10
FcγRIIb1*	no effect	CAMPATH-1, Fog-1, 2D10
FcγRIIIb NA1	remained at background	Fog-1, 2D10
FcγRIIIb NA2	remained at background	Fog-1, 2D10
Monocyte activation	remained at background	Fog-1
Complement lysis	>20-fold reduction to background	CAMPATH-1, 2D10
ADCC	100-fold reduction	CAMPATH-1, Fog-1

iv) Appendix IV - line-ups

Full C_H2 Sequences